UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

005234

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

JUN 30 1986

MEMORANDUM

SUBJECT: Preliminary Review of Combined Toxicity and Oncogenicity Study in Rats on 2,4-Dichlorophenoxy-acetic acid.

FROM: Marcia van Gemert, Ph.D. M. van Gemert 6.30.86
Head, Section III
Toxicology Branch, HED (TS-769C)

TO: Lois Rossi
Special Review Branch
Registration Division (TS-767C)

THRU: Theodore M. Farber, Ph.D. Theodore M. Farber 6/30/86
Chief
Toxicology Branch/HED (TS-769C)

Compound: 2,4-Dichlorophenoxyacetic acid

Tox. Chem. No.: 315

Registrant: Industry Task Force on 2,4-D Research Data

Accession No.: 030001

Action Requested:

Review the toxicology/oncogenicity study submitted on 2,4-dichlorophenoxyacetic acid, possible 6(a)(2) action.

Conclusions:

The administration of 2,4-D appears to produce increased numbers of astrocytomas in brains of male rats at 45 mg/kg/day and is suggestive of a carcinogenic effect. The final determination of oncogenicity will come after a joint review with the Canadian Health Protection Branch, an evaluation of the brain and spinal cord slides by EPA officials, and presentation of the weight of evidence before the EPA Peer Review Committee.

The Task Force that submitted the study to EPA is presently re-evaluating the brain slides by an independent pathologist to confirm the diagnosis of astrocytoma, and will

submit a report of this re-evaluation in July, 1986.

The task force should be requested to submit summary tables for the urinalysis data which were missing from the text of the study. They should also be asked to re-tabulate and submit clearer summary tables of the non-neoplastic and neoplastic lesions. Examples of summary incidence tables are appended to this memo for clarification. The Task Force should also be requested to submit all brain and spinal cord slides of control and experimental animals. Based on the non-neoplastic lesions seen in the kidney, (see DER)

the NOEL = 1 mg/kg/day and the LEL = 5 mg/kg/day.

Core Classification: Will be assigned pending receipt of the requested data.

Reviewed by: Marcia Van Gemert, Ph.D. M. Van Gemert 6.30.86
Section 3, Tox. Branch (TS-769C) Section Head
Secondary reviewer: Theodore M. Farber, Ph.D. Theodore M. Farber
Chief, Tox. Branch (TS-769)

DATA EVALUATION REPORT

STUDY TYPE: Combined toxicity & oncogenicity TOX. CHEM. No.: 315

ACCESSION NUMBER: 263112-263114 MRID No.:

TEST MATERIAL: Dichlorophenoxyacetic acid

SYNONYMS: 2,4-D

STUDY NUMBER(S): 2184-103

SPONSOR: Industry Task Force on 2,4-D Research Data

TESTING FACILITY: Hazleton Labs, 9200 Leesburg Turnpike
Vienna, Virginia 22180

TITLE OF REPORT: Combined Toxicity and Oncogenicity Study in Rats
2,4-Dichlorophenoxyacetic acid, final report

AUTHOR(S): D.G. Serota, Ph.D. - Study Director

REPORT ISSUED: May 29, 1986

CONCLUSIONS: Increased astrocytomas in male rats at 45 mg/kg
NOEL = 1 mg/kg/day
LEL = 5 mg/kg/day based on kidney effects
Classification: Will be assigned pending receipt of the requested information.

A. MATERIALS:

1. Test compound: 2,4-D, Description of test material is on appended pg.1 Purity 97.5%, contaminants: list in CBI appendix

2. Test animals: Species: rats, Strain: CDF(F344)/CRL-BR, Age: 7 wks.
Weight: 125.8-158.3, 94.4-118.5 Source: Charles River Breeding Labs Kingston, New York

B. STUDY DESIGN:

1. Animal assignment - 600 animals were assigned to the following test groups:

TABLE 1

Test Group	Dose in diet mg/kg/day	Main Study 104 wks. male	female	Interim Sac. 53 weeks male	female
1 Cont.	0	60	60	10	10
2 Low (LDT)	1	60	60	10	10
3 Mid-1 (MDT)	5	60	60	10	10
4 Mid-2	15	60	60	10	10
5 High	45	60	60	10	10

2. Diet preparation - Diet was premixed in 200 gms of basal diet and prepared weekly for 1st 14 weeks biweekly through week 18 then every 4th week thereafter and stored at room temperature. Samples of treated food were analyzed for stability and concentrations of 2,4-D in diet for weeks 1, 2, 3, 4, 17, 30, 43, 56, 69, 82, 95.

Results - Analysis of the diet indicated 2,4-D was stable in the diet for at least one month.

TABLE 2

Analysis of 2,4-D Concentrations

Groups	Percentage of Target Range		Mean & S.D.
	Low	High	
2	84.6	120.3	101.96 ± 9.54
3	82.1	125.3	100.6 ± 9.2
4	80.8	122.2	97.8 ± 8.7
5	81.9	113.4	98.1 ± 7.2

3. Animals received food (Diet + 2,4-D) and water ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: (See appended pgs. 2&3).

5. Quality assurance was in compliance with EPA GLP regulations.

C. METHODS AND RESULTS:

1. Observations - Animals were inspected twice/day for signs of toxicity and mortality.

Detailed physical exams for physical appearance, behavior tissue mass palpation and signs of abdominal distention were made weekly for 1st 14 weeks and biweekly thereafter.

Results - Toxicity - no treatment related effects on mortality (survival) were noted. (See appended pages 4 & 5).

TABLE 3

Mortality and (Percent Survival) at Month[a]

		6	12	18	24
			Males		
Group	1	1 (98)	1 (98)	2 (95)	18 (64)
	2	0 (100)	0 (100)	2 (95)	7 (85)
	3	0 (100)	0 (100)	0 (100)	2 (96)
	4	1 (98)	2 (97)	3 (94)	8 (84)
	5	0 (100)	0 (100)	0 (100)	12 (76)
			Females		
	1	1 (98)	2 (97)	4 (92)	10 (80)
	2	0 (100)	0 (100)	1 (98)	13 (74)
	3	0 (100)	0 (100)	0 (100)	2 (96)
	4	1 (98)	2 (97)	3 (94)	8 (84)
	5	0 (100)	0 (100)	0 (100)	12 (76)

a. Percent survival based on 60, 60, 50 and 50 rats/sex/group at 6, 12, 18 and 24 months, respectively.

2. Body Weight - Animals were weighed at initiation of the experiment and weekly for 1-14 weeks then biweekly for remainder of experiment.

Results - Statistical analysis of absolute body weight at week 52, body weight changes at weeks 0-52 and 0-104 and growth rate data showed significantly decreased mean values for group 5 females. (see appended pages 6 & 7 for cumulative body weight gain.)

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TABLE 4

MEAN CUMULATIVE BODY WEIGHT GAIN

	0-52 Weeks females			males			0-104 weeks males		females		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	N	Mean	S.D.
1	58	113.4	11.57	59	229.6	18.30	32	216.8	40	145.6	14.87
2	60	114.1	8.61	60	225.4	17.33	43	211.2	37	142.9	26.0
3	60	116.7	11.77	60	227.1	19.28	48	214.5	38	141.0	22.07
4	60	113.5	12.43	58	232.3	16.88	42	213.9	38	144.8	17.22
5	60	105.2*	11.31	59	227.9	14.05	37	206.5	36	132.8*	17.14

* Significantly different from control $p \leq 0.05$

3. Food consumption and compound intake - Consumption was determined and mean daily diet consumption was calculated. Food consumption was measured weekly for first 14 weeks and then biweekly for the remainder of the experiment.

Results - Food consumption - mean values for Group 5 females were significantly lower than control values at weeks 1 - 52. Also the mean value for Group 2 females was significantly higher than the mean value for Group 1 females at this time interval.

TABLE 5

MEAN TOTAL FOOD CONSUMPTION -Females

	0-52 weeks N	Mean	SD	0-104 weeks N	Mean	SD
1	58	3114.9	169.52	40	5861.8	289.84
2	57	3198.9*	171.65	34	5989.4	313.94
3	56	3174.9	164.39	35	6022.7	319.78
4	60	3115.7	166.14	38	5816.9	304.19
5	60	3038.6*	140.29	35	5751.4	291.19

*Significantly different from control $p \leq 0.05$

4. Ophthalmalogical examinations were performed at end of 52 weeks and at 104 weeks all animals.

Results - Ophthalmic exam revealed no ocular toxicity that could be associated with 2,4-D administration at any dose.

5. Blood was collected before treatment and at 26, 52 and 78 weeks for hematology and clinical analysis from 10 animals/sex/group. Clinical analysis was collected on all animals surviving to termination of study. The checked (X) parameters were examined.

a. Hematology -

X		X	
X	Hematocrit (HCT)*	X	Total plasma protein (TP)
X	Hemoglobin (HGB)*	X	Leukocyte differential count
X	Total leukocyte count (WBC)*		Mean corpuscular HGB (MCH)
X	Erythrocyte count (RBC)*		Mean corpuscular HGB conc. (MCHC)
X	Platelet count*		Mean corpuscular volume (MCV)
X	Reticulocyte count		

Results -

No treatment-related results on the hematological parameters measured were apparent.

b. Clinical Chemistry

X		X	
	Electrolytes:		Other
X	Calcium*	X	Albumin*
	Chloride*		Blood creatinine*
	Magnesium*	X	Blood urea nitrogen*
	Phosphorous*		Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
	Enzymes	X	Total Bilirubin*
X	Alkaline phosphatase		Triglycerides
	Cholinesterase	X	Albumin/globulin ratio
	Creatinine phosphokinase*	X	Thyroxine
X	Lactic acid dehydrogenase	X	Total protein
X	Serum alanine aminotransferase (also SGPT)*		
X	Serum aspartate aminotransferase (also SGOT)*		

Results -

1. there was a slight ($p \leq .05$) increase in the albumin and a slight decrease ($p \leq 0.05$) in globulin at week 105 in males, increasing the A/G ratio at both 79 and 105 weeks ($p < 0.05$). (see appended pages 8 & 9)

2. There was slight ($p \leq 0.05$) increase in serum alanine aminotransferase in males and females at week 105 in Group 5. (see appended page 10)

3. T_4 was slightly depressed ($p \leq 0.05$) at 105 weeks in group 5 females. (see appended page 11)

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6. Urinalysis - Urine was collected from 10 rats/sex/group at initiation and following weeks 26, 52, and 78 weeks of treatment. The CHECKED (X) parameters were examined.

X		X	
	Appearance*	X	Glucose*
	Volume*	X	Ketones*
X	Specific gravity*	X	Bilirubin*
X	pH		Blood*
	Sediment (microscopic)*		Nitrate
X	Protein*	X	Urobilinogen

Results - Tables on mean values for urinalysis were missing from the text.
There appears to be a decrease in urinary protein at the highest dose level. Summary tables will have to be generated before this can be verified.

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

Digestive system		Cardiovasc./Hemat.		Neurologic	
	Tongue		Aorta*	XX	Brain*
X	Salivary glands*	XX	Heart*	X	Periph. nerve* (sciatic)
X	Esophagus*	X	Bone marrow*	X	Spinal cord
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	X	Spleen*	X	Eyes (optic n.)*
X	Jejunum*	X	Thymus*	Glandular	
X	Ileum*	Urogenital		XX	Adrenals*
X	Cecum*	XX	Kidneys*		Lacrimal gland
X	Colon*	X	Urinary bladder*		Mammary gland*
	Rectum*	XX	Testes*	XX	Parathyroids*
XX	Liver*	XX	Epididymides	XX	Thyroids*
	Gall bladder*	X	Prostate	Other	
X	Pancreas*		Seminal vesicle	X	Bone*(sternum with marrow)
Respiratory		XX	Ovaries	X	Skeletal muscle*
X	Trachea*	X	Uterus*	X	Skin
X	Lung*			X	All gross lesions and masses

Summaries of the pathology protocols for the 52-week sacrifice, unscheduled deaths, and the terminal sacrifices are appended on pages 12 and 13. The study states that "brain" sections (including at least one section of the forebrain, mid brain and hind brain) were examined microscopically by the study pathologist and then read blind by a second pathologist. Following these examinations remaining fixed brain tissue from each animal

was processed and evaluated microscopically by the study pathologist. These observations were incorporated into the original findings to yield a composite incidence from both evaluations.

I called Dr. David Sorota of Hazelton Laboratories, the Study Director, and asked specifically how the brain was sectioned. He said originally only one section from fore, mid and hind brain was examined. But after finding some astrocytomas, they then sectioned all available brain tissue from each rat. We are in the process of formally writing to the Task Force for written confirmation of this statement.

Results -

a. Organ Weight

Interim sacrifice

Kidney weight parameters measured, eg. absolute organ weight, organ-to-body weight, and organ-to-brain weight were significantly elevated in the group 5 males. Females showed a slight increase in kidney weight parameters no other significant organ weight changes were noted. (see table 6 for details.)

TABLE 6

ORGAN WEIGHTS 52 WEEK SACRIFICE

		Absol. Wts		organ-to body wts.		organ-to-brain wts.	
Kidney Male	#	Mean	SD	Mean	SD	Mean	SD
1	10	2.44	.17	.693	.043	1.225	.061
2	10	2.43	.11	.684	.022	1.214	.041
3	10	2.46	.26	.698	.050	1.225	.107
4	10	2.61	.12	.738	.037	1.295	.053
5	10	2.66*	.15	.780*	.057	1.344*	.091
Kidney Female							
1	10	1.57	.10	.805	.090	0.876	.046
2	10	1.62	.13	.802	.067	0.901	.055
3	10	1.56	.10	.785	.052	0.873	.069
4	10	1.62	.05	.784	.036	0.892	.034
5	10	1.60*	.09	.829*	.037	0.884	.048

*Significantly different from controls $p \leq 0.05$

Terminal Sacrifice

At 105 weeks there was an increase in kidney weight parameters in groups 4 and 5 with statistical

significance in the females ($p \leq 0.05$) in group 5 in all parameters. (Table 7) The increases in kidney weight values appear to be treatment-related. There appeared to be a dose-related increase at 104 weeks in all male thyroid/parathyroid parameters with statistical significace generally in groups 4 and 5. In female there appeared to be a trend of increased values in groups 3, 4, and 5 with group 4 having statistical significance. This appears to be a treatment-related effect. The other organ weights that were significantly different from control were noted in group 5. These organs include liver and thyroids/parathyroids in males, pituitary, brain with brain stem, and ovaries in females. Those changes in the pituitary, liver and ovaries appear treatment-related.

TABLE 7

ORGAN WEIGHTS 104 WEEK SACRIFICE

		Absolute Organ wt.		Organ-to-Body wt.		Organ-to-Brain wt.	
LIVER Male	N	Mean	SD	Mean	SD	Mean	SD
1	32	10.02	2.02	2.996	.664	4.846	.962
2	43	9.66	1.14	2.956	.390	4.702	.560
3	47	9.94	1.69	2.992	.538	4.827	.814
4	41	9.41	1.25	2.837	.337	4.609	.592
5	36	8.82	1.29	2.730	.543	4.277*	.658
LIVER Female							
1	40	7.14	1.35	3.072	.638	3.811	.658
2	37	7.16	0.95	3.102	.487	3.812	.483
3	37	7.07	1.20	3.099	.509	3.799	.626
4	38	7.04	1.15	3.061	.488	3.755	.578
5	36	6.73	1.23	3.066	.599	3.577	.620
KIDNEYS combined-Male							
1	32	2.78	0.35	.829	.111	1.345	.177
2	43	2.75	0.32	.840	.112	1.338	.169
3	47	2.74	0.31	.825	.090	1.333	.154
4	41	2.84	0.34	.860	.113	1.393	.162
5	36	2.85	0.26	.880	.111	1.383	146
KIDNEYS combined-Female							
1	40	1.89	0.14	.813	.066	1.012	.081
2	37	1.95	0.13	.844	.095	1.037	.071
3	37	1.98	0.20	.871*	.108	1.064	.107
4	38	1.94	0.16	.843	.061	1.034	.088
5	36	2.07*	0.30*	.945*	.195	1.099*	.161
PITUITARY Male							
1	32	.022	.023	.0067	.0076	.0106	.0114
2	43	.016	.006	.0048	.0016	.0077	.0027
3	47	.024	.026	.0074	.0076	.0119*	.0124
4	41	.028	.066	.0092	.0252	.0139	.0351
5	36	.018	.015	.0055	.0045	.0086	.0075

TABLE- 7 CONT.

PITUITARY Female							
1	40	.016	.010	.0069	.0039	.0086	.0053
2	37	.023	.026	.0103	.0141	.0120	.0134
3	37	.040*	.071	.0180*	.0321	.0220*	.0386
4	38	.021	.033	.0087	.0121	.0112	.0177
5	36	.033*	.052	.0157*	.0278	.0176*	.0280
BRAIN $\bar{w}$ STEM Male							
1	32	2.07	.06	.618	.041		
2	43	2.06	.06	.629	.033		
3	47	2.06	.07	.620	.042		
4	41	2.04	.08	.618	.052		
5	36	2.07	.11	.638	.062		
BRAIN w STEM Female							
1	40	1.87	.06	.805	.063		
2	37	1.88	.06	.816	.088		
3	37	1.86	.08	.820	.082		
4	38	1.87	.06	.818	.068		
5	36	1.88	.06	.857*	.077*		
OVARIES							
1	39	.108	.039	.0467	.0176	.0582	.0215
2	36	.105	.040	.0456	.0184	.0560	.0215
3	37	.125	.067	.0538	.0247	.0670	.0354
4	38	.115	.034	.0504	.0168	.0612	.0184
5	36	.131	.060	.0589*	.0260	.0693	.0320
THYROID/PARATHYROID Male							
1	32	.027	.009	.0082	.0027	.0133	.0043
2	41	.031	.009	.0094	.0029	.0150	.0046
3	46	.032	.011	.0097	.0034	.0157	.0054
4	41	.033*	.007	.0100*	.0020	.0163*	.0036
5	36	.034	.014	.0106*	.0041	.0166	.0063
THYROID/PARATHYROID Female							
1	40	.025	.006	.0106	.0028	.0131	.0033
2	37	.024	.007	.0105	.0037	.0128	.0038
3	37	.027	.005	.0117	.0023	.0143	.0027
4	38	.031*	.008	.0134*	.0035	.0164*	.0044
5	35	.027	.009	.0123	.0042	.0144	.0048

b. Gross Pathology

Inspection of detailed gross necropsy findings revealed that there were no differences in incidence of the findings between the control and treated animals with unscheduled deaths, at the 52 week sacrifice, or at the terminal sacrifice.

c. Microscopic Pathology

1) Non-neoplastic

52-Week Sacrifice

There were general alterations in histopathological parameters in the kidneys of groups 3, 4, and 5 that appeared compound-related. These consisted of:

1) An increased incidence in brown tubular cell pigment in the males of groups 3, 4 and 5 (9/10, 10/10, 10/10 respectively) and groups 3, 4 and 5 females (5/10, 6/10 and 7/10 respectively) when compared to control males (2/10) and control females (3/10).(Note appended page 14 for details)

2) An increased frequency and severity of fine vacuolization of cytoplasm in the renal cortex in group 5 females (8/10) when compared to control females (5/10) and an increase in severity in groups 3 & 4 females when compared with control females. (see appended page 14 for details on increased severity.)

Unscheduled Deaths

No compound-related histopathologic alterations were found in the animals that died or were killed moribund prior to the terminal sacrifice.

Terminal Sacrifice

Compound-induced histomorphologic alterations occurred in the kidneys of groups 3, 4 and 5 males and females. (These are summarized on table 8.)

These were:

1) Increased brown tubular cell pigment in the kidneys of groups 3, 4 and 5 males (8/47, 18/41**, 18/36** respectively) and groups 3, 4 and 5 females (23/37*, 19/38**, 13/36 respectively) when compared to control males (2/32) and females (8/40).(Note appended page 15 for statistical analysis)

2) Increased incidence of pelvic microcalculi in groups 4 and 5 males (8/41, 9/36 respectively) and group 5 females (28/36**) when compared to control males (2/32) and female (19/40).

3) A slight increase in frequency of transitional epithelial hyperplasia in group 5 females (6/36) when compared to controls (0/40) however, the study pathologists considered this secondary to the increased frequency of microcalculi.

TABLE 8

NON-NEOPLASTIC LESIONS IN RATS FED 2,4-D

Tubular Cell Pigment, increased kidney	Males					Females				
	1	2	3	4	5	1	2	3	4	5
UD*	0	1	1	0	1	0	1	0	1	2
IS**	2	2	9	10	10	3	3	5	6	7
TS***	2	0	8	18	18	8	9	23	19	13
Total	4	3	18	28	29	11	13	28	26	22
Transitional Epithelial Hyperplasia										
US	0	0	0	0	3	1	1	0	2	5
IS	0	0	0	0	0	2	1	1	3	3
TS	0	1	1	1	0	0	0	3	2	6
Total	0	1	1	1	3	3	2	4	7	14
Microcalculi Pelvis										
UD	0	0	1	0	2	0	2	1	2	7
IS	0	1	0	0	1	2	3	1	3	4
TS	2	2	3	8	9	19	9	14	21	28
Total	2	3	4	8	12	21	14	16	26	39
Fine cytoplasmic Vacuolization										
UD	0	0	0	0	0	0	0	0	0	0
IS	0	0	0	0	0	5	3	5	5	8
TS	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	5	3	5	5	8

*UD = unscheduled deaths
**IS = Interim sacrifice
***TS = Terminal sacrifice

2) Neoplastic

Astrocytomas were found in the brains of rats with unscheduled deaths and terminal sacrifice, including a group 1 male that died in week 21 and two group 4 males that were killed in extremis in week 94 and 105, and one group 5 male that was killed in extremis in week 93. There were no reported astrocytomas found in the 52-week interim sacrifice but at the 104-week terminal sacrifice, 5 astrocytomas were found in group 5 males and none in the other four groups. The total astrocytomas found for male rats on test then totaled 1/60 for group 1 controls, with 0/60, 0/60, 2/58 and 6/60 for groups 2,3,4 and 5 respectively. .(See appended

pages 17,18 and 19 for summary tables and individual animal data). According to the study text,"The incidence of astrocytomas in the brain of high-dose males is higher than that in control males, intercurrent mortality adjusted prevalence analysis indicates a positive trend at p = 0.0026 (one-tailed, uncorrected score test), and control versus high-dose group comparison is significant at p = 0.0351 (one-tail); but not at two-tail (p = 0.0702). (See appended page 20 for statistical analysis).

D. DISCUSSION:

comments:

1. The administration of 2,4-D appears to produce astrocytomas in brains of male rats at 45 mg/kg/day dose level, and is suggestive of a carcinogenic effect. The task force that submitted the study for EPA review is presently re-reviewing the diagnoses of the brain slides and will submit another independent pathology report some time in July, 1986. This task force should be asked to submit summary tables for the urinalysis data and compile concise summary incidence tables for all the non-neoplastic and neoplastic histopathology data. They should also be requested to furnish EPA with all control and treated brain and spinal cord slides for our own independent analysis.

2. Based on the increase in frequency and/or severity of kidney lesions seen in groups 3, 4 and 5 male and female rats the NOEL for non-neoplastic lesions is 1 mg/kg/day, the LEL = 5 mg/kg/day.

TS-769:VAN GEMERT:6/25/86

cc. W. Burnam
T. Farber
A. Barton
J. Melone
J. Lamb
J. Moore

Appendix P71

INDUSTRY TASK FORCE ON 2,4-D RESEARCH DATA

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"Contains or relates to trade secrets, confidential or proprietary information of the industry task force on 2, 4-D research data."

Analysis of 2,4-D Blend Used For Toxicity Testing

[redacted]

"Contains or relates to trade secrets, confidential or proprietary information of the industry task force on 2, 4-D research data."

HAZLETON
LABORATORIES AMERICA, INC.
9200 LEESBURG TURNPIKE, VIENNA VIRGINIA 22180 U.S.A.

Statistical Analyses

Cumulative survival data through Week 104 were analyzed using the National Cancer Institute Package. Trend analysis of survival was evaluated at the 5.0% one-tailed probability level.

Growth rates (rates of body weight gain) were compiled using body weight values from Weeks 0, 1, 4, 9, 20, and 52 for males and Weeks 0, 2, 5, 10, 26, and 52 for females (Rao, 1958).

Absolute body weights at Weeks 52 and 104, body weight changes between Weeks 0 and 52 and Weeks 0 and 104, growth rates, total food consumption through Weeks 52 and 104, clinical pathology data (except differential leukocyte count, cell morphology, and urinalysis), and organ weight data of the control group were compared statistically to the data from the same sex of the treated groups. Statistical analyses were performed as diagrammed in Figure 1.

If variances of untransformed data were heterogeneous, analyses were performed on transformed data to achieve variance homogeneity. When the series of transformations were not successful in achieving variance homogeneity, analyses were performed on rank-transformed data. The criterion for significance of group comparisons was at the 5.0% two-tailed probability level.

Neoplastic lesions were analyzed for unadjusted incidences by Cochran-Armitage test for trend and Fisher Irwin exact test for heterogeneity (Thakur et al, 1985). Further adjusted analysis of these lesions were performed by the prevalence method of Dinse and Lagares (1983). Graded non-neoplastic incidences were analyzed for trend and heterogeneity by the RIDIT method (Bross, 1958; Selvin, 1977).

Specimen, Raw Data, and Final Report Storage

Specimens, raw data, and the final report are stored in the archives of Hazleton Laboratories America, Inc.

2184-103

FIGURE 1

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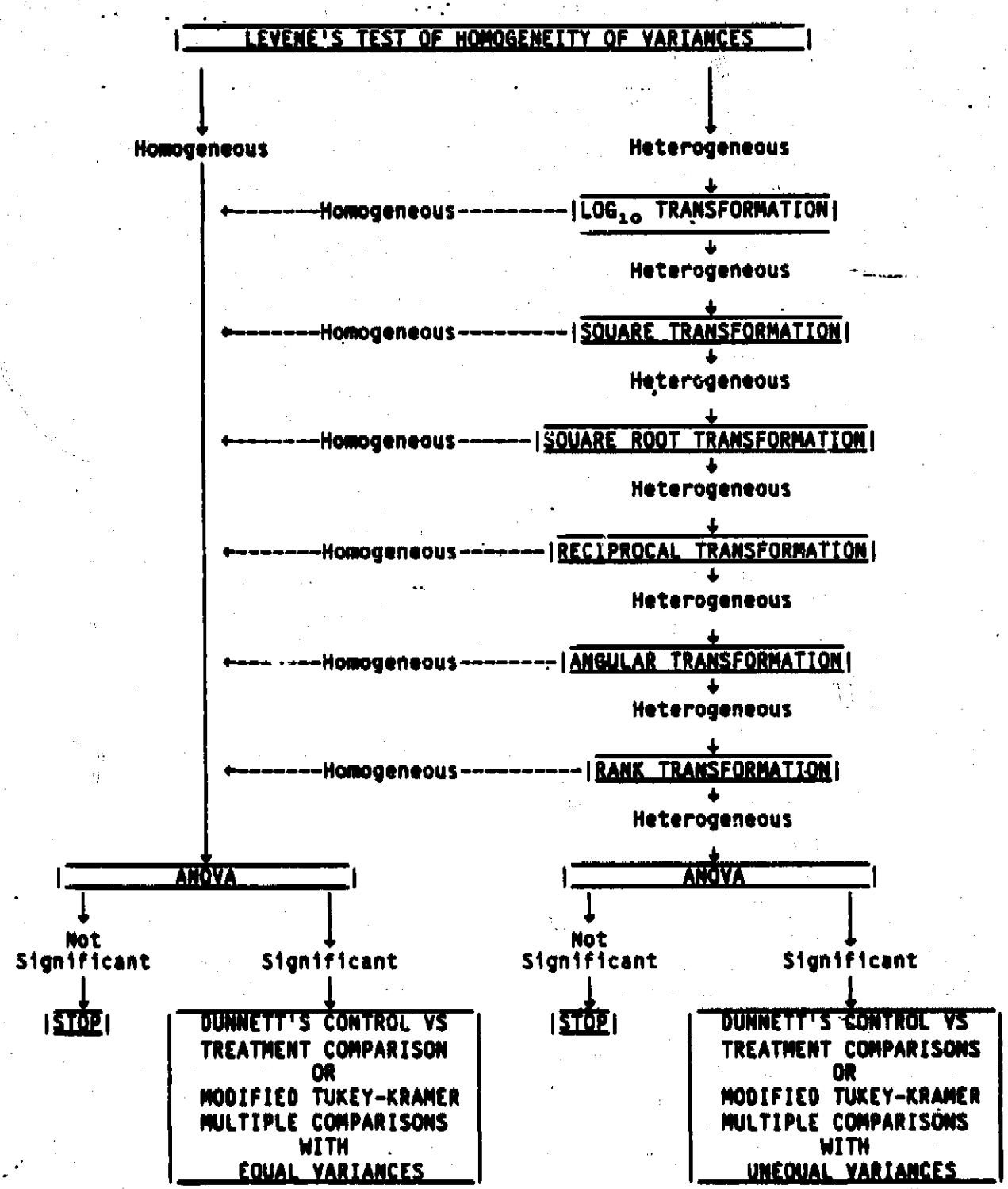

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FIGURE 2 – ADJUSTED SURVIVAL

FEMALES 2184–103

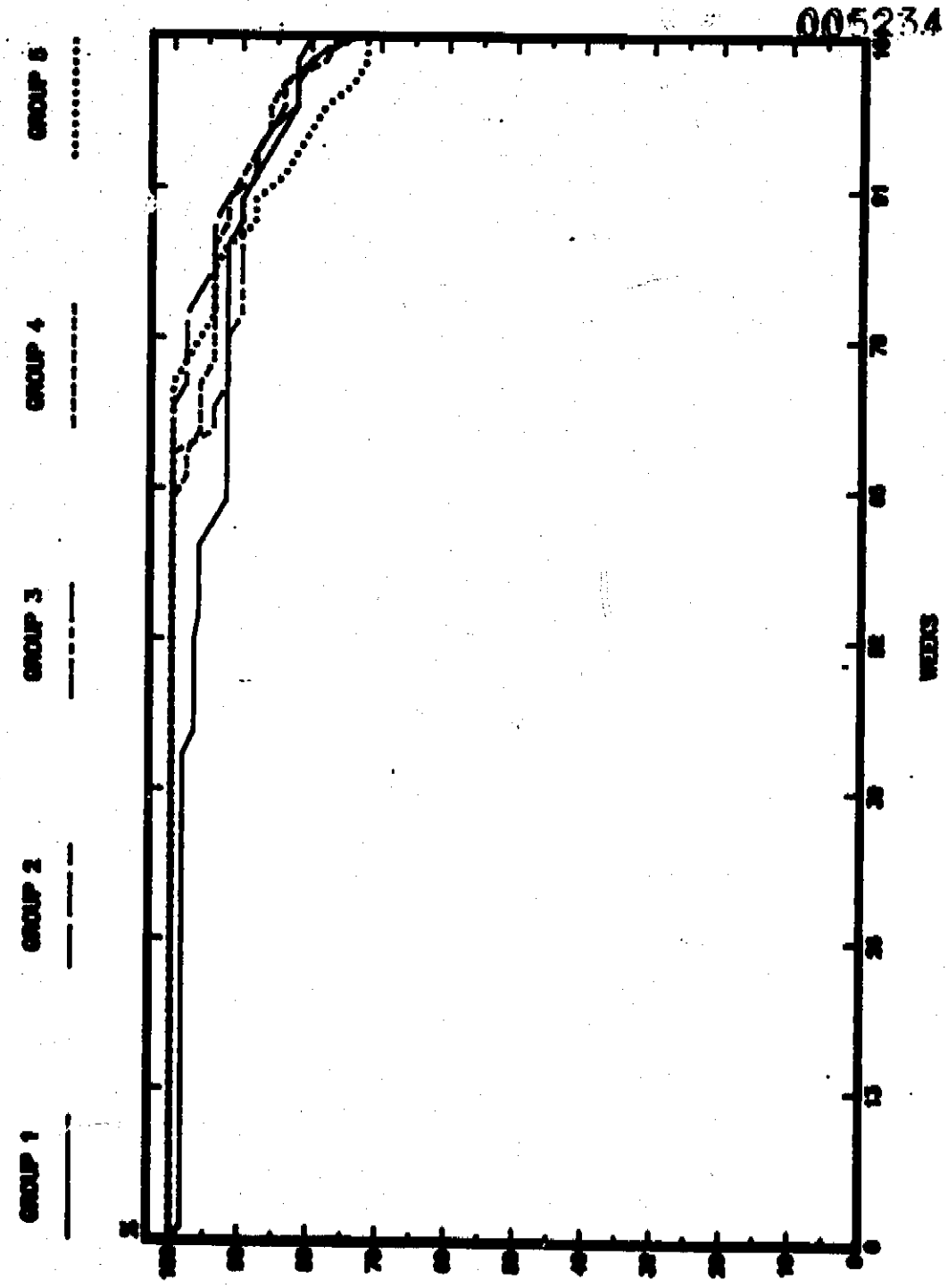

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FIGURE 2 -- ADJUSTED SURVIVAL

MALES 2184-103

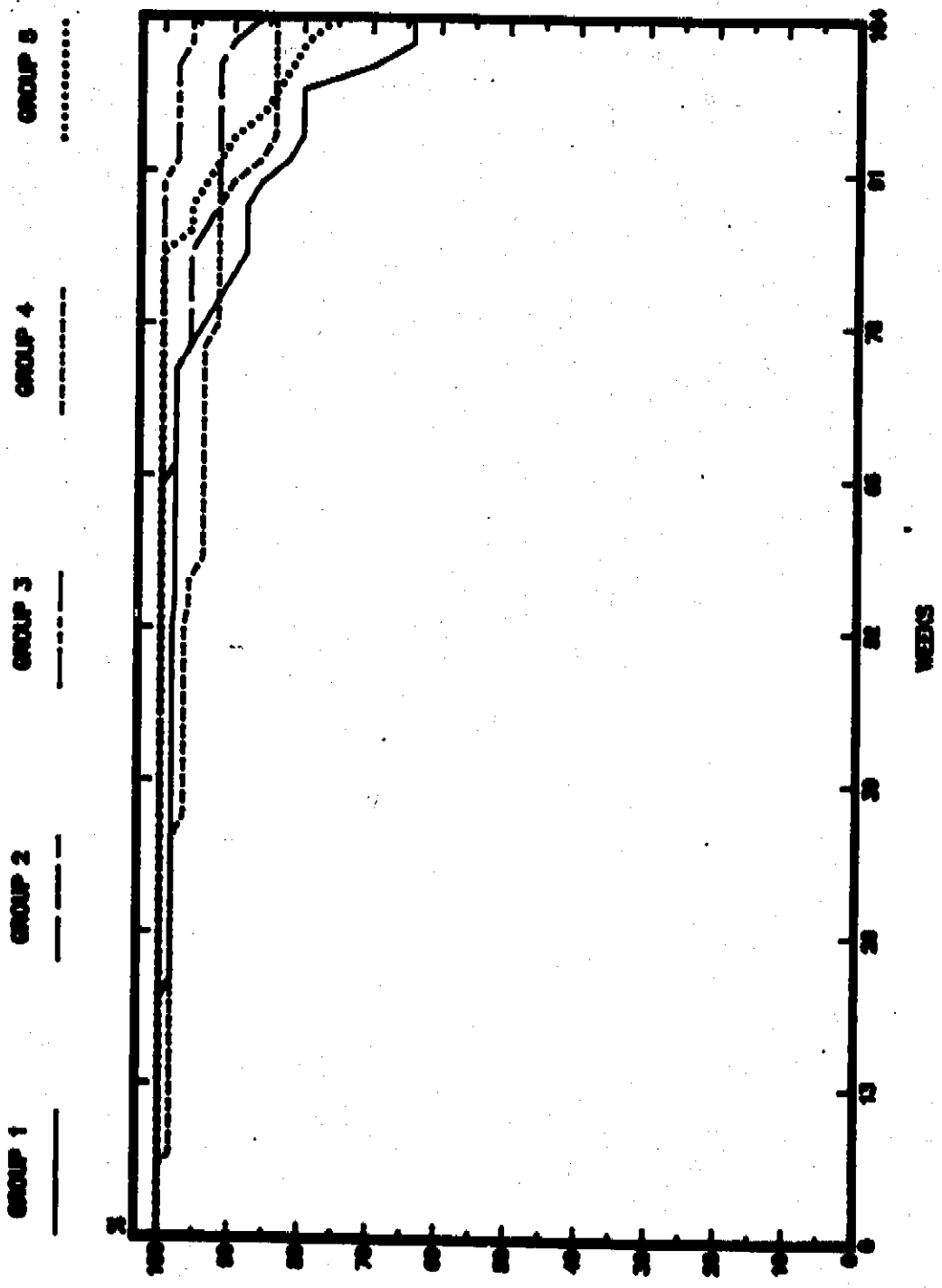

FIGURE 3 – MEAN BODY WEIGHTS

MALES 2184–103

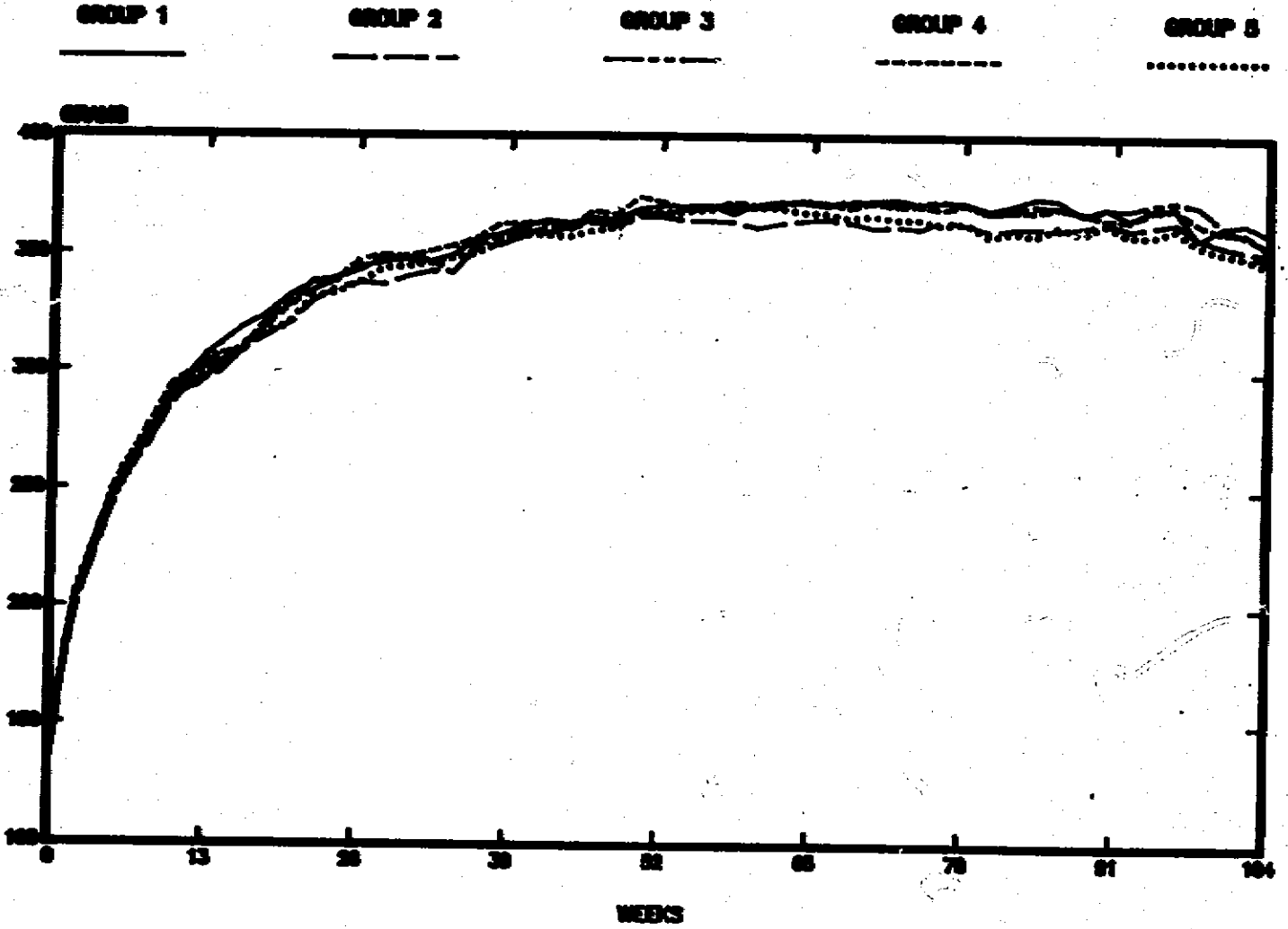

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FIGURE 3 – MEAN BODY WEIGHTS

FEMALES 2184–103

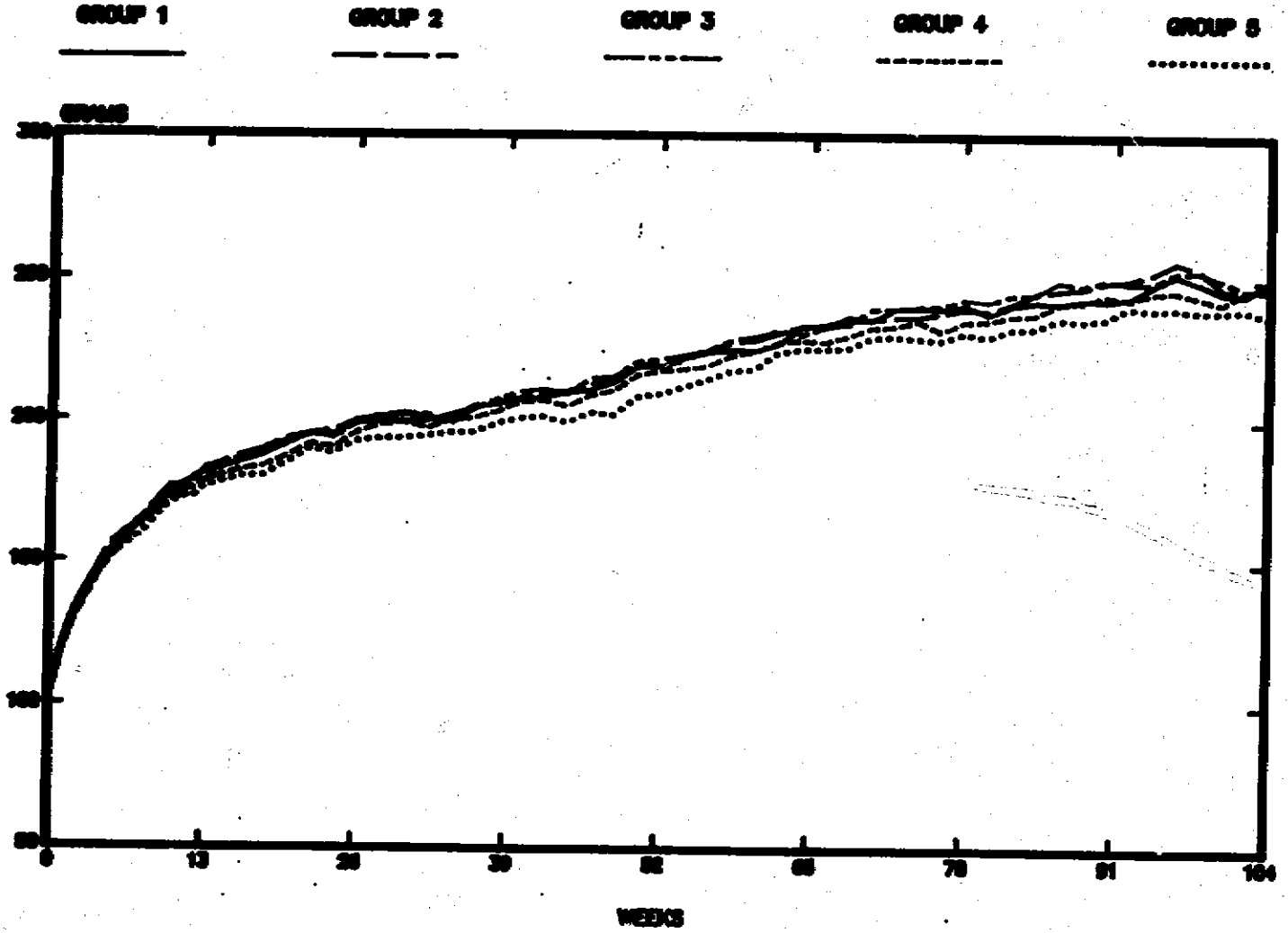

TABLE B - CONTINUED
MEAN CLINICAL CHEMISTRY VALUES
COMBINED CHRONIC TOXICITY AND ONCOGENICITY STUDY IN RATS

GROUP AND DOSAGE LEVEL		T PROT G/DL WEEK 0	27[a]	53	79	105[b]	ALBUMIN G/DL WEEK 0	27	53	79	105
MALE											
1 CONTROL	MEAN	5.4	6.3	6.8	6.1	6.3	3.6	3.8	3.4	3.4	3.6
	S.D.	.24	.28	.25	.27	.49	.17	.12	.18	.14	.33
	N	10	10	10	10	32	10	10	10	10	32
2 1.0 MG/KG	MEAN		6.3	6.8	6.8	6.3		3.8	3.5	3.4	3.6
	S.D.		.21	.27	.22	.36		.15	.19	.19	.29
	N		10	10	10	43		10	10	10	43
3 5.0 MG/KG	MEAN		6.3	6.8	6.8	6.4		3.8	3.5	3.5	3.7
	S.D.		.15	.27	.23	.46		.18	.16	.13	.26
	N		10	10	10	45		10	10	10	46
4 15.0 MG/KG	MEAN		6.3	5.7	6.1	6.2		3.7	3.4	3.5	3.7
	S.D.		.21	.37	.25	.43		.13	.18	.16	.35
	N		10	10	10	41		10	10	10	41
5 45.0 MG/KG	MEAN		6.8	5.8	6.1	6.3		3.6*	3.4	3.5	3.9*
	S.D.		.32	.19	.28	.43		.18	.07	.21	.34
	N		10	10	10	36		10	10	10	36
FEMALE											
1 CONTROL	MEAN	5.4	6.4	6.6	6.3	6.8	3.6	4.1	3.9	3.7	4.2
	S.D.	.16	.20	.37	.29	.33	.18	.13	.23	.17	.26
	N	10	10	10	10	40	10	10	10	10	40
2 1.0 MG/KG	MEAN		6.4	6.6	6.3	6.6		4.0	3.9	3.6	4.1
	S.D.		.32	.34	.39	.53		.25	.25	.31	.36
	N		10	10	10	37		10	10	10	37
3 5.0 MG/KG	MEAN		6.6	6.6	6.5	6.6		4.1	3.9	3.8	4.1
	S.D.		.25	.29	.33	.71		.14	.16	.28	.40
	N		10	10	10	37		10	10	10	37
4 15.0 MG/KG	MEAN		6.4	6.4	6.5	6.7		4.1	3.8	3.8	4.2
	S.D.		.11	.77	.22	.30		.09	.58	.15	.31
	N		10	10	10	38		10	10	10	38
5 45.0 MG/KG	MEAN		6.3	6.4	6.4	6.8		4.0	4.0	3.8	4.2
	S.D.		.31	.19	.28	.37		.17	.13	.19	.34
	N		10	10	10	34		10	10	10	34

[a] Analysis was performed on square transformed data for males.
[b] Analysis was performed on rank transformed data for females.
* Significantly different from control, $p \leq .05$.

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TABLE 8 - CONTINUED
MEAN CLINICAL CHEMISTRY VALUES
COMBINED CHRONIC TOXICITY AND ONCOGENICITY STUDY IN RATS

GROUP AND DOSAGE LEVEL		GLOBULIN G/DL WEEK 0	27[a]	53	79	105	A/G RATIO WEEK 0	27[a]	53	79	105
					MALE						
1 CONTROL	MEAN	1.8	2.4	2.6	2.7	2.6	2.83	1.56	1.31	1.29	1.40
	S.D.	.13	.21	.21	.28	.35	.146	.120	.100	.098	.210
	N	10	10	10	10	32	10	10	10	10	32
2 1.0 MG/KG	MEAN		2.5	2.5	2.6	2.6		1.54	1.37	1.32	1.41
	S.D.		.09	.12	.15	.35		.059	.070	.116	.220
	N		10	10	10	43		10	10	10	43
3 5.0 MG/KG	MEAN		2.5	2.5	2.5	2.7		1.52	1.39	1.38	1.42
	S.D.		.11	.14	.13	.33		.075	.061	.062	.179
	N		10	10	10	45		10	10	10	45
4 15.0 MG/KG	MEAN		2.6	2.3	2.6	2.5		1.45*	1.47	1.36	1.48
	S.D.		.11	.33	.10	.34		.061	.208	.100	.306
	N		10	10	10	41		10	10	10	41
5 45.0 MG/KG	MEAN		2.4	2.4	2.5	2.4*		1.51	1 45	1.42*	1.63*
	S.D.		.15	.17	.17	.34		.056	.097	.119	.291
	N		10	10	10.	36		10	10	10	36
					FEMALE						
1 CONTROL	MEAN	1.8	2.3	2.7	2.6	2.5	2.84	1.75	1.47	1.39	1.71
	S.D.	.18	.15	.19	.18	.27	.119	.118	.094	.080	.252
	N	10	10	10	10	40	10	10	10	10	40
2 1.0 MG/KG	MEAN		2.4	2.6	2.6	2.5		1.67	1.51	1.39	1.64
	S.D.		.11	.15	.35	.36		.084	.106	.229	.289
	N		10	10	10	37		10	10	10	37
3 5.0 MG/KG	MEAN		2.5	2.7	2.7	2.4		1.68	1.46	1.41	1.71
	S.D.		.14	.14	.19	.37		.081	.053	.096	.294
	N		10	10	10	37		10	10	10	37
4 15.0 MG/KG	MEAN		2.3	2.6	2.7	2.5		1.77	1.47	1.48	1.78
	S.D.		.10	.20	.20	.27		.097	.087	.126	.260
	N		9	10	10	38		10	10	10	38
5 45.0 MG/KG	MEAN		2.3	2.6	2.6	2.4		1.73	1.51	1.42	1.67
	S.D.		.19	.15	.14	.38		.120	.103	.088	.253
	N		10	10	10	34		10	10	10	34

[a] Analysis was performed on rank transformed data for males.
* Significantly different from control, $p \leq .05$.

TABLE 8 - CONTINUED
MEAN CLINICAL CHEMISTRY VALUES
COMBINED CHRONIC TOXICITY AND ONCOGENICITY STUDY IN RATS

GROUP NO. DOSAGE LEVEL		AST U/L WEEK 0	27	53	79[a]	105[a]	ALT U/L WEEK 0	27[b]	53	79	105[a,b]
						MALE					
1 CONTROL	MEAN	87	73	108	84	73	28	46	48	59	44
	S.D.	7.7	13.3	19.5	23.6	47.5	5.2	5.3	13.5	26.8	32.7
	N	9	10	10	10	31	10	10	10	10	31
2 1.0 MG/KG	MEAN		81	126	105[c]	77		53	84	68[c]	44
	S.D.		14.1	44.1	109.1	63.8		12.9	39.6	45.9	30.5
	N		10	10	10	42		10	10	10	42
3 5.0 MG/KG	MEAN		78	97	74	74		44	67	49	45
	S.D.		15.1	23.8	7.9	68.7		6.5	16.9	5.9	48.5
	N		10	10	10	45		10	10	10	45
4 15.0 MG/KG	MEAN		82	98	78	91		57	73	48	39
	S.D.		23.8	24.3	15.6	27.8		25.1	16.4	6.7	13.8
	N		10	10	10	41		10	10	10	41
5 45.0 MG/KG	MEAN		71	102	77	127		66*	73	53	69*
	S.D.		16.4	30.6	14.4	269.4		12.1	23.6	7.9	87.4
	N		10	10	10	35		10	10	9	36
						FEMALE					
1 CONTROL	MEAN	83	83	108	76	68	27	52	68	46	44
	S.D.	13.5	8.7	32.4	24.9	39.8	2.3	8.3	17.5	7.4	19.2
	N	10	10	10	10	48	10	10	10	10	48
2 1.0 MG/KG	MEAN		76	86	64	69		49	59	42	47
	S.D.		11.1	22.8	12.5	64.7		12.7	20.3	10.5	40.3
	N		10	10	10	36		10	10	10	36
3 5.0 MG/KG	MEAN		76	96	65	75		39*	73	44	58
	S.D.		7.6	20.6	13.4	64.1		4.6	22.3	7.2	32.4
	N		10	10	10	37		10	10	10	37
4 15.0 MG/KG	MEAN		70*	82	61	112		46*	57	41	63
	S.D.		4.3	13.8	8.2	168.2		4.5	17.4	4.8	48.9
	N		10	10	10	38		10	10	10	38
5 45.0 MG/KG	MEAN		79	97	72	98		47	75	51	63*
	S.D.		12.6	8.6	13.2	103.2		8.2	13.8	11.1	48.2
	N		10	10	10	34		10	10	10	34

[a] Analysis was performed on $\log_{10}$ transformed data for males (and females [AST] at Week 105).

[b] Analysis was performed on rank transformed data for females.

[c] Additional statistical analyses were performed excluding the values for animal No. 23110; the specimen was icteric. Results were as follows: AST MEAN = 70, S.D. = 13.4 analysis performed on rank transformed data, no significance revealed; ALT MEAN = 46, S.D. = 8.0 analysis performed on rank transformed data, no significance revealed.

TABLE 8 - CONTINUED
MEAN CLINICAL CHEMISTRY VALUES
COMBINED CHRONIC TOXICITY AND ONCOGENICITY STUDY IN RATS

GROUP AND DOSAGE LEVEL		LDH U/L WEEK 0	LDH U/L WEEK 27	LDH U/L WEEK 53	LDH U/L WEEK 79	LDH U/L WEEK 105	T4 UG/DL WEEK 0	T4 UG/DL WEEK 27[a]	T4 UG/DL WEEK 53	T4 UG/DL WEEK 79	T4 UG/DL WEEK 105
MALE											
1 CONTROL	MEAN	545	363	225	251	162	7.47	5.0	4.5	4.1	3.7
	S.D.	114.5	79.2	88.6	104.8	82.6	.943	.43	.78	.71	1.12
	N	10	10	10	10	32	10	10	10	10	32
2 1.0 MG/KG	MEAN		435	281	217	142		4.5	4.2	3.7	3.5
	S.D.		43.4	91.1	129.0	103.2		.46	.68	.91	.92
	N		10	10	10	43		10	10	10	43
3 5.0 MG/KG	MEAN		391	238	249	153		5.3	4.2	3.8	3.6
	S.D.		73.7	67.5	65.2	92.6		.33	.48	.97	1.05
	N		10	10	10	47		10	10	10	46
4 15.0 MG/KG	MEAN		353	257	269	159		5.3	4.1	3.6	3.8
	S.D.		74.3	106.9	142.3	74.7		.73	.52	.87	.96
	N		10	10	10	41		10	10	9	41
5 45.0 MG/KG	MEAN		387	234	284	158		5.2	4.1	3.2	3.6
	S.D.		53.6	119.9	124.5	111.4		.79	.49	.91	.95
	N		10	10	10	35		10	10	10	36
FEMALE											
1 CONTROL	MEAN	379	319	155	164	187	4.27	3.1	2.5	2.4	3.3
	S.D.	84.2	79.9	45.8	72.7	57.9	.464	.53	.45	1.06	1.84
	N	10	10	10	10	48	10	10	10	9	48
2 1.0 MG/KG	MEAN		260	162	162	99		3.6	2.8	2.5	3.5
	S.D.		52.2	64.5	42.3	46.0		.60	.61	.53	1.17
	N		10	10	10	37		9	10	8	37
3 5.0 MG/KG	MEAN		282	169	165	116		3.6	2.8	2.6	3.1
	S.D.		77.2	47.2	128.3	71.1		.58	.69	.67	1.14
	N		10	10	10	37		10	10	10	36
4 15.0 MG/KG	MEAN		211*	171	125	101		3.8	3.3*	2.6	3.8
	S.D.		54.5	65.7	47.5	518.3		.67	.68	.68	.73
	N		10	10	10	38		10	10	10	38
5 45.0 MG/KG	MEAN		250	169	131	122		3.8	2.3	2.2	2.7*
	S.D.		39.5	79.6	34.8	189		.38	.75	.75	.86
	N		10	10	10	36		10	10	10	36

[a] Analysis was performed on $\log_{10}$ transformed data for males.

* Significantly different from control, $p \leq .05$.

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PATHOLOGY SUMMARY
52 Week Interim Sacrifice

General Protocol

Six-hundred, six to seven week old Fischer 344 rats, 300 males and 300 females, were assigned computer generated random numbers and placed in one of five groups of 60 males and 60 females each. Group 1 served as the control group. Groups 2, 3, 4 and 5 served as the low-, mid-1-, mid-2-, and high-dose groups receiving 1, 5, 15 and 45 mg/kg/day respectively, of the test compound 2,4-Dichlorophenoxyacetic acid (2,4-D) in their diet.

Following 52 weeks of treatment, 10 animals per sex, per group (last ten in each group) were anesthetized with a barbiturate, exsanguinated and necropsied with the following tissues collected and preserved in 10% neutral buffered formalin: brain, eyes with Harderian gland, pituitary, salivary gland, heart, thymus, thyroid with parathyroids, lungs, trachea, esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, adrenals, pancreas, liver, kidneys, urinary bladder, testes with epididymides, prostate (males), ovaries, uterine horns and body (females), spleen, mesenteric lymph nodes, skin, sciatic nerve, mammary gland, sternum with marrow, skeletal muscle, three levels of the spinal cord, nasal passage/cavity, nasopharynx, paranasal sinus, tongue, oral cavity, middle ear, and gross lesions. The above underlined tissues were weighed. The above tissues except for three levels of the spinal cord, nasal passage/cavity, nasopharynx, paranasal sinus, tongue, oral cavity and middle ear, were embedded in Paraplast®, sectioned at 5-6 μ, placed on glass slides and stained with hematoxylin and eosin and coverslipped and then examined by a board-certified veterinary pathologist.

Histopathology

Compound-induced, dose-related histomorphologic tissue alterations occurred in the kidneys of Groups 3 (5 mg/kg), 4 (15 mg/kg) and 5 (45 mg/kg) male and female rats. These alterations consisted of: 1) an increased

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2184-103

PATHOLOGY SUMMARY
Unscheduled Deaths and Terminal Sacrifices

General Protocol

Six-hundred, six to seven week old Fischer 344 rats, 300 males and 300 females, were assigned computer generated random numbers and placed in one of five groups of 60 males and 60 females each. Group 1 served as the control group. Groups 2, 3, 4 and 5 served as the low-, mid-1-, mid-2-, and high-dose groups receiving 1, 5, 15 and 45 mg/kg/day respectively, of the test compound 2,4-Dichlorophenoxyacetic acid (2,4-D) in their diet.

Following 104/105 weeks of treatment, all surviving animals were anesthetized with a barbiturate, exsanguinated and necropsied with the following tissues collected and preserved in 10% neutral buffered formalin: brain, eyes with Harderian gland, pituitary, salivary gland, heart, thymus, thyroid with parathyroids, lungs, trachea, esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, adrenals, pancreas, liver, kidneys, urinary bladder, testes with epididymides, prostate (males), ovaries, uterine horns and body (females), spleen, mesenteric lymph nodes, skin, sciatic nerve, mammary gland, sternum with marrow, skeletal muscle, three levels of the spinal cord, nasal passage/cavity, nasopharynx, paranasal sinus, tongue, oral cavity, middle ear, and gross lesions. The above underlined tissues were weighed. The preserved tissues except for three levels of the spinal cord, nasal passage/cavity, nasopharynx, paranasal sinus, tongue, oral cavity and middle ear from unscheduled deaths and all but the last 10 terminal sacrificed animals in each dose group; and the preserved tissues except the lumbar spinal cord from the last 10 terminal sacrificed animals in each dose group were embedded in Paraplast®, sectioned at 5-6 μ, placed on glass slides and stained with hematoxylin and eosin and coverslipped and then examined by a board-certified veterinary pathologist. In addition, all original brain sections were randomized and read "blind" by another Hazleton Senior Pathologist. Subsequent to these evaluations of three sections of brain per animal, three to five sections of remaining fixed brain tissue from each animal were processed and evaluated microscopically by the study pathologist. Therefore a total of six to eight brain sections were examined microscopically for each animal.

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Text Table
KIDNEY
Incidence of Increased Tubular Cell Pigment
and Fine Vacuolization of the Cytoplasm in the Renal Cortex

	MALES					FEMALES				
Number examined	1/10	2/10	3/10	4/10	5/10	1/10	2/10	3/10	4/10	5/10
Increased tubular cell pigment										
Present	2	2	9	10	10	3	3	5	6	7
Fine vacuolization of the cytoplasm in the renal cortex										
Not observed	10	10	10	10	10	5	7	5	5	2
Minimal	0	0	0	0	0	2	0	1	0	2
Slight	0	0	0	0	0	3	3	1	1	1
Moderate	0	0	0	0	0	0	0	3	4	5

Statistical Summary Table 2
Unadjusted Incidence Data

Parameter	Sex	Cochran-Armitage Test Trend p	Direction	Departure p	Overall Heterogeneity p	Groups	Fisher-Irwin Exact Test Direction	1-tail p	2-tail p
KIDNEYS:									
Tubular Cell Pigment	M	.0000**	FT	.0075**	.0000**	1 vs 4	+	.0003**	.0004**
						1 vs 5	+	.0001**	.0001**
Tubular Cell Pigment	F	.5241	FT	.0002**	.0005**	1 vs 3	+	.0002**	.0002**
						1 vs 4	+	.0052**	.0052**

** Significant at 1% level
FT Fluctuating trend, direction cannot be determined

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Statistical Summary Table 1
Relative to an Identified
Distribution (RIBIT) Analysis

Parameter	Sex	Groups†	Direction	Control vs Treated Comparison 1-tailed α	2-tailed α
KIDNEYS:					
Microcalculi	F	1 vs 5	+	.0017**	.0033**

** Significant at 1% level
† Only Group 5 was elevated compared to control.

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Text Table 1
Incidence of astrocytomas in the brain of F-344 rats receiving 2,4-Dichlorophenoxyacetic acid at 0, 1, 5, 15, or 45 mg/kg/day

	Male					Female				
Group:	1	2	3	4	5	1	2	3	4	5
Mg/Kg/Day 2,4-D:	0	1	5	15	45	0	1	5	15	45
Unscheduled Deaths:	1/18	0/7	0/3	2/7	1/14	0/10	1/13	0/13	0/12	0/14
Post Week 52 Interim Sacrifice:	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Post Week 104/105 Terminal Sac.	0/32	0/43	0/47	0/41	5/36	0/40	0/37	2/37	1/38	1/36
All Animals on Study:	1/60	0/60	0/60	2/58	6/60	0/60	1/60	2/60	1/60	1/60

Characteristics of Primary Brain Neoplasms in F344 Rats on a Two-Year 2,4 - Dichlorophenoxyacetic Acid Feeding Study

Terminal (104/105 Week) Sacrifice

Group	Dose mg/kg/day	Animal Number	Sex	Diagnosis	Location[1]	Size[2]	Pattern of Infiltration[3]	Cellular Pleomorphism	Other Features
1	0	23024	M	Granular Cell Tumor	M,C(midline)	S	C	minimal	Nodular and compressive. Cells with eosinophilic cytoplasmic granules. No mitoses.
5	45	23473*	M	Astrocytoma	C(t)	M	Pc	slight	Small round, oval to spindle nuclei, perivascular cuffing. No mitoses.
5	45	23476	M	Astrocytoma	Cb,M	L	D	slight	Small round to oval nuclei, cavitation, hemosiderin. No mitoses.
5	45	23479	M	Astrocytoma	C(t)	M	Pc	slight	Small round to oval nuclei, perivascular cuffing. No mitoses.
5	45	23492	M	Astrocytoma	C(p,t),M	L	D	slight	Small round to oval nuclei, hemosiderin. Moderate mitoses.
5	45	23500	M	Astrocytoma	C(f)	L	D	minimal	Small round nuclei, perivascular cuffing. Few mitoses.
3	5	23205*	F	Astrocytoma	Ob	S	Pc	minimal	Oval to spindle nuclei. No mitoses.
3	5	23302	F	Astrocytoma	C(t)	S	Pc	minimal	Small round to oval nuclei. Minimal mitoses.
4	15	23442	F	Astrocytoma	C(f,p)	L	D	minimal	Small round to oval nuclei, perivascular cuffing, minimal necrosis and hemosiderin. No mitoses.
5	45	23546	F	Astrocytoma	C(midline)	L	D	slight	Small round to spindle nuclei, perivascular cuffing. Many mitoses.

[1] C = Cerebrum (f = frontal, p = parietal, t = temporal, o = occipital); Cb = Cerebellum; H = Hippocampus, M = Meninges; Bs = Brain stem; Ob = Olfactory bulb.
[2] S (small) = <2mm; M (medium) = 2 - 4mm; L (large) = > 4mm.
[3] C = Circumscribed; Pc = Poorly circumscribed; D = Diffuse.
* Tumors found in newly embedded brain tissue but not present in originally embedded brain tissue.

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Characteristics of Primary Brain Neoplasms in F344 Rats on a Two-Year 2,4 - Dichlorophenoxyacetic Acid Feeding Study

Group	Dose mg/kg/day	Animal Number	Sex	Diagnosis	Location[1]	Size[2]	Pattern of Infiltration[3]	Cellular Pleomorphism	Other Features
Found Dead and Sacrificed									
1	0	23025	M	Astrocytoma	C(t,p,o),M	L	D	minimal	Small round nuclei, necrosis, cavitation, hemorrhage, perivascular cuffing. Few mitoses.
4	15	23376	M	Astrocytoma	C(o)	M	Pc	minimal	Small round to oval nuclei, perivascular cuffing. No mitoses.
4	15	23377	M	Astrocytoma	C(f,p,t) (bilateral)	L	D	slight	Small round to oval nuclei, necrosis, hemosiderin, perivascular cuffing, meningeal infiltration. Minimal mitoses.
5	45	23505*	M	Astrocytoma	Ob	S	Pc	slight	Small round to spindle nuclei, perivascular cuffing, meningeal infiltration. Minimal mitoses.
2	1	23185	F	Astrocytoma	Bs	M	Pc	minimal	Small round to oval nuclei, perivascular cuffing. No mitoses.

[1] C = Cerebrum (f = frontal, p = parietal, t = temporal, o = occipital); Cb = Cerebellum; H = Hippocampus, M = Meninges; Bs = Brain stem; Ob = Olfactory bulb.
[2] S (small) = <2mm; M (medium) = 2 - 4mm; L (large) = > 4mm.
[3] C = Circumscribed; Pc = Poorly circumscribed; D = Diffuse.
* Tumors found in newly embedded brain tissue but not present in originally embedded brain tissue.

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Statistical Summary Table 3
Adjusted Astrocytoma Incidence Data

Sex	Interval	Trend p	Direction	Groups	Direction	1-tail p	2-tail p
M	All	0.0026**	+	1 vs 5	+	0.0351*	0.0702

* = Significant at 5% level
** = Significant at 1% level

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SAMPLE SHEET

EVERY PATHOLOGY REPORT SHOULD HAVE INDIVIDUAL:
HISTOPATHOLOGY INCIDENCE TABLE

005234

Male Mice
Scheduled Sacrifices

Group 1

ANIMAL NUMBER	168-456	168-457	168-458	168-459	168-460	168-461	168-462	168-463	168-464	168-465	168-466	168-467	168-468	168-469	168-470	168-471	168-472	168-473	168-4
LUNG		X				X	X				X			X	X		X	X	X
Alveolar/Bronchiolar Carcinoma																			
Malignant Lymphoma																			
Malignant Lymphoma, Undifferentiated																			
Alveolar/Bronchiolar Adenoma								p		p									
Carcinoma, Metastatic																			
Granulocytic Leukemia																			
Sarcoma, Metastatic					p														
Multifocal Pleuritis																			
Multifocal Pneumonitis			2																
Alveolar Macrophages, Pigmented																1			
Focal Alveolar/Bronchiolar Hyperplasia																			
Congestion																			
Focal Hemorrhage								3											
Alveolar Macrophages																			
Foci of Foamy Macrophages																			
Leukocytosis																			
Peribronchial/Vascular Mononuclear Cells	1		1	1							2	1				1			
Alveolar Proteinosis																			
Multifocal Alveolar-Bronchiolitis	1															1			

SAMPLE SHEET

EVERY PATHOLOGY REPORT SHOULD HAVE:
SUMMARY INCIDENCE TABLE

emale Mice

	Group 1			Group 5			Group 6			Group 7		
	Scheduled Sacrifice	Moribund Sacrifice & Death	Total	Scheduled Sacrifice	Moribund Sacrifice & Death	Total	Scheduled Sacrifice	Moribund Sacrifice & Death	Total	Scheduled Sacrifice	Moribund Sacrifice & Death	Total
UNG (NO. EXAMINED)	(43)	(7)	(50)	(42)	(8)	(50)	(38)	(12)	(50)	(39)	(11)	(5
Alveolar/Bronchiolar Carcinoma	2		2	2		2	2		2	3		3
Malignant Lymphoma					1	1		4	4		1	1
Malignant Lymphoma, Undifferentiated		2	2				1		1		1	1
Alveolar/Bronchiolar Adenoma	3		3	3		3	5	2	7	4		4
Carcinoma, Metastatic	1	1	2		1	1		2	2			
Granulocytic Leukemia					1	1						
Sarcoma, Metastatic												
Multifocal Pleuritis							1		1	3		3
Multifocal Pneumonitis	5		5	2		2	4		4	3		3
Alveolar Macrophages, Pigmented	7		7	4		4				1	1	2
Focal Alveolar/Bronchiolar Hyperplasia	2		2	2		2	2		2	1		1
Congestion	2	2	4	4	5	9	3	5	8	3	8	1
Focal Hemorrhage				2		2	1		1	1		1
Alveolar Macrophages	2		2	2		2	2		2	1		1
Foci of Foamy Macrophages	4		4	3		3				2		2
Leukocytosis				1	2	3					3	3

END